REMARKS / ARGUMENTS

Claims 1, 2 and 4-12 are pending in the application and stand rejected. The Applicants previously submitted a Response on June 30, 2010. In an Advisory Action mailed July 13, 2010 (the "Advisory Action"), The Examiner entered the amendments and withdrew the rejection of claim 12 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner maintained the obviousness and double patenting rejections. In view of the following discussion, the applicants submit that all pending claims are in condition for allowance.

The Examiner maintained the rejection of claims 1-2, 4, 6 and 12 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al., (U.S. Pat. No. 6,261,539); over Lewis et al. (EP 1219293); and over Ashurst et al. (U.S. Pat. No. 6,511,652); and claims 1-2, 4 and 6 as being unpatentable over Keller et al. (U.S. Pat. 6,475,467). For the reasons discussed below, and those discussed in previous responses incorporated herein by reference, none of the references teach or suggest the subject matter of claim 1. A showing that the claimed range achieves unexpected results relative to the prior art range rebuts a *prima facie* case of obviousness based on claimed ranges that overlap or lie inside ranges disclosed by the prior art. *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). None of the references teach or suggest the claimed range of water of claim 1 to result in a significantly better single actuation reproducibility (SAR) for "cans" containing albuterol sulfate and ipratropium bromide with a water content of 1300 to 1800 ppm to release the same amount of albuterol sulfate (i.e., % of theory) during each single actuation event. None of these references would lead a skilled artisan to conclude the claimed range of water content would have a significant effect on the SAR.

In the Advisory Action the Examiner did not find the previous arguments to be persuasive, contending the data submitted in the Declaration of George DeStefano ("DeStefano Declaration") submitted March 20, 2008 does not show unexpected results. The Examiner contends that (1) standard deviation is not a support for unexpected result; (2) in a formulation the criticality is its function as a formulation and unexpected results show unexpected bioavailability of the formulation, and that a showing of consistency of spraying is not support for bioavailability; and (3) even if standard deviation was to be accepted as a showing of unexpected result, there is no showing here as the standard deviations produced by the applicant in the reply of 01/14/10 are not all accurate. The applicants address each contention below.

Contentions (1) and (2) were previously discussed in the Response submitted June 30, 2010. As to contention (1), MPEP § 716.02(b)(I) supports the use of standard deviation or other statistical analysis may be used to show unexpected and unobvious results. As to contention (2), a skilled artisan desiring to deliver consistent doses of an active substance to a patient via an actuator would consider the consistency of actuator events as critical in obtaining consistent bioavailability.

The Examiner's support for contention (3) is the assertion that the "standard deviation of the upright can 5 containing 1200 ppm for albuterol is 15.69 while the same can containing 1500 ppm for albuterol has a standard deviation of 16.8". We have reviewed the data submitted in the DeStefano Declaration and the standard deviations we calculated differ from those asserted (i.e., 15.69 and 16.8) by the Examiner. Specifically, when the standard deviations of separate cans were calculated, there was an unexpectedly large difference between cans containing 1200 ppm water for albuterol as compared to cans containing 1500 ppm water for albuterol. For example, the calculated standard deviations for inverted can nos. 1-5 containing 1200 ppm for albuterol are 18.22, 15.34, 18.36, 18.57 and 17.06, respectively (data taken from page 8 of the DeStefano Declaration). In contrast, the calculated standard deviation for inverted can nos. 1-5 containing 1500 ppm for albuterol are 6.56, 3.28, 7.12, 6.52 and 7.14, respectively (data taken from page 10 of the DeStefano Declaration). The calculated standard deviations for upright can nos. 6-10 containing 1200 ppm for albuterol are 51.13, 48.97, 49.87, 45.86 and 52.56, respectively, as compared to the calculated standard deviations for upright can nos. 6-10 containing 1500 ppm for albuterol which are 7.93, 5.96, 10.64, 5.12 and 6.61 (data taken from pages 9 and 11 of the DeStefano Declaration).

Additionally, the calculated standard deviations for inverted can nos. 1-5 containing 1200 ppm for albuterol are 23.10, 22.62, 27.42, 19.42 and 24.79, respectively as compared to the calculated standard deviations for inverted can nos. 1-5 containing 1500 ppm for albuterol which are 9.89, 13.16, 5.83, 8.21 and 6.25, respectively (data taken from tables 5 and 6 on pages 35-36 of the DeStefano Declaration). The calculated standard deviations for upright can nos. 1-5 containing 1200 ppm for albuterol are 20.49, 20.07, 32.08, 29.35 and 41.22, respectively as compared to the calculated standard deviations for upright can nos. 1-5 containing 1500 ppm for albuterol which are 5.92, 8.07, 7.55, 6.58 and 8.36, respectively (data taken from tables 5 and 6 on pages 35-36 of the DeStefano Declaration).

Finally, the calculated standard deviations for inverted can nos. 1-5 containing 1200 ppm for albuterol are 2.67, 1.74, 1.68, 1.49 and 3.57, respectively as compared to the calculated standard deviations for inverted can nos. 1-5 containing 1500 ppm for albuterol which are 0.9, 1.04, 1.36, 0.97 and 0.58, respectively (data taken from tables 11 and 12 on pages 42-43 of the DeStefano Declaration). The calculated standard deviations for upright can nos. 1-5 containing 1200 ppm for albuterol are 3.58, 1.68, 10.07, 1.92 and 10.16, respectively as compared to the calculated standard deviations for upright can nos. 1-5 containing 1500 ppm for albuterol which are 1.34, 2.06, 2.01, 2.39 and 1.09, respectively (data taken from tables 11 and 12 on pages 42-43 of the DeStefano Declaration).

As shown above, the data in the DeStefano Declaration clearly shows that fluctuations of the single actuation events are very different between certain cans of differing water contents and that the formulations in cans containing 1500 ppm and above of water were unexpectedly superior in terms of actuation reproducibility to cans containing 1200 ppm water or less. Fluctuation between single actuation events was unexpectedly reduced in both inverted and upright cans containing 1500 ppm. As previously discussed, the analysis illustrates that the consistency of % reproducibility in cans having a water content of 1500 ppm was superior to cans having water content of 1200 ppm or below. This comparison clearly indicates that simply adding water above inherent levels does not always result in improved consistency. It was unexpected that such a large improvement of consistency of % reproducibility could have been achieved at water content levels at or above 1500 ppm.

In light of the above discussion, the data presented in the DeStefano Declaration clearly illustrates the unexpected superiority of the claimed water content in the reproducibility of actuation events. One skilled in the art viewing any one of Adjei, Ashurst, Lewis or Keller would not expect that water content as claimed would have such a profound effect on actuation reproducibility. Water content is not identified in any of the prior art references as an important factor for this characteristic. One skilled in the art would be led to believe water content is not an important factor in achieving reproducibility. Thus, claim 1 is not obvious in light of the prior art references. Claims 2, 4, 6 and 12 which depend from amended claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejections.

The Examiner rejected claims 5 and 7-11 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al. in view of Jager et al. (WO 9413262); and as being unpatentable over Lewis et al. in view of Jager et al. (WO 9413262). For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, the combination of the references does not result in the claimed invention. Neither Adjei alone or in combination with Jager nor Lewis alone or in combination with Jager teach or suggest the claimed range of water of the invention of claim 1 to result in a significantly better SAR for "cans" containing albuterol sulfate and ipratropium bromide with a water content of 1300 to 1800 ppm to release the same amount of albuterol sulfate (i.e., % of theory) during each single actuation event. None of these references would lead a skilled artisan to conclude the claimed range of water content would have a significant effect on the SAR. Since the combinations of Adjei and Jager as well as Lewis and Jager do not result in claim 1, dependent claims 5 and 7-11 cannot be obvious over Adjei in view of Jager or Lewis in view of Jager and are thus allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejections.

The Examiner rejected claims 1-2, 4-12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Pat. No. 6,423,298 in view of Adjei et al. The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, claim 1 is not obvious over the combination of the references. The combination of the references cannot teach a skilled artisan the claimed water content that results in unexpected actuation reproducibility as discussed above. Therefore, the combination of the '298 patent and Adjei does not result in the claimed invention. Thus, claims 1, 2 and 4-12 are not obvious over the '298 patent in view of Adjei and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

Applicants submit that all claims pending in the patent application are in condition for allowance. Accordingly, entry of this amendment, reconsideration of this application and its swift passage to issuance are earnestly solicited. The fees for a RCE and a three month extension are included herewith. In the event there are any fees due and owing in connection with this matter, please charge same to our Deposit Account No. 11-0223.

Respectfully submitted,

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